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Hormonal Therapy in Gynecologic Malignancy

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ABSTRACT
In endometrial cancer, hormonal therapy is used for treatment of endometrioid histologies. Because endometrial stromal sarcoma also expresses estrogen (ER) and progesterone (PR) receptors, adjuvant targeted hormonal treatment is beneficial to reduce recurrence. Combination hormonal therapy for advanced or recurrent endometrial cancer is an attractive treatment alternative for selected patients, especially those with hormone receptor–positive tumors. The potential response rate and the low toxicity profile associated with these agents make them a suitable therapeutic first choice for many such patients. A significant proportion of ovarian cancers including both epithelial and stromal varieties express both estrogen and/or progesterone receptors so, hormonal therapy has role in treatment of such cancer. The most commonly used agents are progestens, tamoxifen, luteinizing hormone-releasing hormone and aromatase inhibitors.

Keywords
Hormonal therapy, Ovarian cancer, Endometrial cancer.

Hormonal therapy in treatment of endometrial cancer
Incidence and epidemiology
Endometrial cancer is the most common gynecological malignancy in North America. Number of estimated new cases in United States, 2019, was 61,880 cases and number of estimated deaths is 12,160 cases [1]. Uterine sarcomas are uncommon malignancies accounting for approximately 3 % of all uterine cancer [2].

Types of endometrial carcinoma according to estrogen dependence
Pathological subtypes according to estrogen dependence: (1) Type I (estrogen related), the more common type of endometrial carcinoma, is associated with diabetes mellitus and obesity, and tends to have better prognosis. Characteristics include the following: a) endometrioid histology. b) more differentiated, lower grade, higher progesterone receptor (PR) levels. c) younger patients. c) less myometrial invasion, lower stage at presentation. d) genetic aberrations as: microsatellite instability, DNA mismatch repair defects, mutations in K-ras, b-catenin, PI3K. (2) Type II (unrelated to estrogen stimulation and endometrial hyperplasia),

it has the following criteria: a) nonendometrioid histology (serous, clear cell). b) serous type is commonly associated with p53 mutations. c) Her2/neu overexpressed. d) aneuploidy [3].

Pathological types of endometrial cancer
Pathological subtypes are: (1) epithelial carcinoma (such as, pure endometrioid cancer, papillary serous carcinoma, clear cell carcinoma, or carcinosarcoma, which is also known as malignant mixed Müllerian tumor [MMMT]); or (2) stromal/mesenchymal tumors (such as, low-grade endometrial stromal sarcomas [ESSs], high-grade undifferentiated sarcoma [HGUD], or leiomyosarcoma [LMS]) [4].

Pathogenesis of endometrial cancer and hormone
Oestrogens work as typical tumour promoters in the formation of type1 carcinoma. Through mitogenic activity, they increase the probability of endometrial hyperplasia, with possible progressive transformation to (mostly well-differentiated) carcinoma. Further mutations (in the p53-gene, loss of the expression of oestrogen and progesterone receptors, among other things) favour the transformation to more aggressive malignant, undifferentiated carcinoma with correspondingly worse prognosis [3]. It has recently been recognised that particular oestrogen metabolites (as

active estradiol, estrone) are significant in the genesis of hormone-dependent tumours. Therefore, the importance of inhibiting the synthesis of these bioactive steroids is desirable in future therapies [5].

Adjuvant hormonal therapy for stage I endometrial cancer
About 75% of patients present with stage I disease, which is confined to the uterus [6].Primary surgical treatment for patients with stage I endometrial cancer typically consists either of a total abdominal hysterectomy with bilateral salpingo-oophorectomy, or complete surgical staging, which involves abdominal hysterectomy, bilateral salpingo-oophorectomy, dissection or sampling of pelvic or para-aortic nodes (or both), peritoneal cytology, omentectomy, and peritoneal biopsies [7]. Between 1983 and 1989, a randomized trial of 388 patients who received either medroxyprogesterone acetate (MPA) or tamoxifen orally for 2 years, or were observed only after surgical therapy was conducted. The aim was to evaluate whether an adjuvant treatment can improve disease-free and overall survival rates. After a median follow-up period of 56 months (range 3-199 months), there was no differences in the disease-free and overall survival rates for the tamoxifen group compared with the control or the MPA group. Side-effects were more frequent and severe in the MPA-group than in the tamoxifen group. Therefore, the conclusion was; in patients with early endometrial cancer, adjuvant endocrine treatment did not significantly improve the outcome [8]. This finding is comparable to that reported in other studies [9-13]. However, Urbanski, et al. [14] detected a statistically significant difference in overall survival between the treatment group who received hydroxyprogesterone caproate, and the control group, who received no further treatment. The most common minor side effects of hormonal therapy included weight gain, peripheral edema and nausea [8,10].

Serious side effects included thromboembolic events such as deep vein thrombosis, pulmonary embolus, and stroke, or cardiovascular disease such as myocardial infarction and deterioration of congestive heart failure. In the trials that reported these events, there were no statistically significant differences reported between the treatment and control groups [9-12]. One trial [8] indicated a serious side effect rate of 6% in the progestogen group as compared with 2% in the control group (p value not reported), and another trial [11] reported higher rates of death from cardiovascular disease in the first 2 years in the progestogen group than in the control group (5% vs. 3%, p = 0.07).The combined treatment (levonorgestrel-release intrauterine device (LNG-IUD) plus gonadotropin-releasing hormone (GnRH) showed effectiveness in a substantial proportion of women aged <40 years with atypical endometrial hyperplasia (AEH) or presumed International Federation of Gynecology and Obstetrics stage IA limited to the endometrium, well differentiated (G1), endometrioid endometrial cancer (EC), who wish to preserve their fertility. Close follow-up during and after treatment is crucial [15].

The results of Perri et al. [16] retrospective study support long-term high-dose progestational therapy as an alternative to hysterectomy for patients whose priority is fertility preservation.

Treatment comprised oral high-dose progestins with or without a levonorgestrel-releasing intrauterine device. Endometrial biopsy was repeated every 2 to 3 months. This treatment combined with ovulation induction or in vitro fertilization-embryo transfer offers patients the chance to achieve more than 1 full-term delivery. Hysterectomy might be deferred until childbearing is completed with no detectable impact on survival. Patients should be advised of the high recurrence rate and possible concomitant ovarian malignancy. Reliable predictors of outcome are being developed to guide conservative therapy. These will undoubtedly be based on further studies of patient and tumor characteristics, for instance, overexpression of p53 and Ki-67, which seems to indicate a more malignant phenotype, which will make it possible to predict, with reasonable confidence, the safety of prolonged conservative treatment for individual patients.

Hormonal therapy for recurrent and advanced endometrial carcinoma
Although progestogens have been the mainstay of hormonal treatment in women with recurrent/metastatic endometrial cancer for many years, these agents are associated with significant adverse effects as mentioned before. These can potentially worsen the quality of life and may be life threatening [17]. These progestational agent have similar mechanism of action which including, reduction of pituitary FSH / LH secretion and stimulation of estrogen and androgen degradation [18].

Five randomized trials and 29 phase II studies were identified comprising a total of 2471 patients. In previously untreated patients with grade 1 (G1) or G2 tumors, the response rate for progestagen and the progression-free survival was in the range of 11-56% and 2.5-14 months, respectively. Higher response rates are seen in progesterone receptor-positive cases. G3 or G4 toxicity was less than 5% [19]. Tamoxifen also has documented single-agent activity in 10% to 20% of women when given first line, but is much lower in the second-line setting [20].

In postmenopausal women, the principal source of estrogen is through conversion of androstenedione by aromatase in peripheral adipose tissue. In addition to peripheral aromatization, aromatase is elevated in endometrial cancer stroma, and locally produced estrogen may act in a paracrine fashion to stimulate cancer growth [21]. However, the response rates to aromatase inhibitors in recurrent and metastatic endometrial cancer have been low (10% objective responserates). But in the reported studies, most patients have had high-grade, hormone receptor negative cancers, where a low likelihood of response would be expected [22].

Combined hormonal therapy
Combination hormonal therapy for advanced or recurrent endometrial cancer is an attractive treatment alternative for selected patients, especially those with hormone receptor–positive tumors. The potential response rate and the low toxicity profile associated with these agents make them a suitable therapeutic first choice for many such patients [23].

Phase II study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma by a Gynecologic Oncology Group study reported the results of 61 patients with measurable advanced or recurrent endometrial carcinoma enrolled on this study to be treated with tamoxifen 40 mg p.o. daily plus alternating weekly cycles of MPA 200 mg p.o. daily. The percent of patients responding was 33% among patients who received therapy. So, the combination of daily tamoxifen and intermittent weekly medroxyprogesterone acetate is an active treatment for advanced or recurrent endometrial carcinoma [24].

Combined Chemo-hormonal Therapy

The earlier trials failed to show that simultaneous chemotherapy and hormonal therapy is superior to the more traditional treatment strategy of using hormonal therapy followed by chemotherapy at the time of disease progression. The most recent trials are promising. However, the question of whether these regimens are better than paclitaxel-containing combination chemotherapy is not known and will require further investigation through a randomized trial [25].

Luteinizing hormone-releasing hormone receptors (LHRH-Rs) mediate antiproliferative activity in endometrial cell lines, and approximately 80% of ECs express LHRH-Rs, providing a potentially useful target in these tumors [26]. Zoptarelin doxorubicin is an [DLys6] LHRH linked to doxorubicin, with activity in LHRH-R-positive cancer cell lines [27]. Zoptarelin doxorubicin induces apoptosis without activating the MDR-1 efflux pump system and it is less toxic than doxorubicin. Following zoptarelin doxorubicin administration in 43 patients with LHRH-R-positive advanced EC, The overall objective response and stable disease rates were 23% and 47%, respectively. [28].

Hormonal therapy for uterine Sarcoma

Uterine sarcomas are uncommon tumors (3% of all uterine neoplasms). They are stromal/ mesenchymal tumors include endometrial stromal sarcomas (ESSs), adenosarcoma and leiomyosarcoma (LMS) which is the most common type (2).

A large proportion of ESSs is ER positive and PR positive, and durable responses to progestogens have been reported [29,30]. So hormone therapy has become standard of care in patients with metastatic ESSs [31]. Tamoxifen is contraindicated in these patients as there have been reports of stimulation of growth due to the partial ER agonist effect of tamoxifen [32]. Leuprolide is an example of the GnRH analogues that have been used in the treatment of pre-menopausal patients with endometriosis and those with breast cancer. These drugs reduce and suppress ovarian estrogen production. Studies have shown successful reduction of stage I sarcomas with leuprolide use [33]. Aminoglutethimide has been reported to be active, and 2 patients with lung metastases had complete responses for 14 and 7 years, respectively [30]. There is significant percentage of ESSs express estrogen receptors as well as estrogen producing enzyme aromatase cytochrome P450. Patients with measurable disease and metastatic ESSs should be considered for treatment with an aromatase inhibitor. In addition,

patients who are at high risk of progression, either following resection of metastases or surgical debulking, and have small volume, nonmeasureable disease should also be considered for treatment with an aromatase inhibitor [34]. Although hormonal therapy has not been widely used to treat women with uterine LMS, hormonal therapy may play role in patients with ER-/PR-positive metastatic LMS who are not suitable for aggressive chemotherapy regimens or after relapse after chemotherapy [35].

Hormonal therapy and ovarian cancer

Ovarian cancer is the second most common gynecological malignancy and the leading cause of death from a gynecological cancer. Estimated number of new cases of ovarian cancer and deaths of ovarian cancer in the US is 22,530 and 13,980 case respectively in 2019(1). Ovarian cancer represents tumors of epithelial, germ cell, or sex cord stromal origin. Approximately 90% of ovarian cancer is epithelial in origin that mostly presented in the advanced stage at diagnosis. While other types of ovarian cancer such as germ cell and sex cord stromal tumors are often localized at presentation and have a more favorable prognosis [36]. There is considerable variability in the reported frequency of ER and PR expression in ovarian cancer between various histological subtypes, with 43% of serous ovarian cancers being both ER and PR positive, but only 16% of borderline serous ovarian tumors were ER positive and 20% were PR positive [37].

A Cochrane Database systematic review of tamoxifen in unselected women with recurrent ovarian cancer reported a 10% objective response and a 32% disease stabilization rate [38]. However, patients treated were very heterogeneous. A Gynecologic Oncology Group (GOG) study reported a 13% objective response rate with tamoxifen in patients with platinum refractory disease with a median response duration of 4.4 months [39]. Tamoxifen is commonly used to treat asymptomatic patients with a rising CA125, an approach supported by retrospective studies that have suggested that tamoxifen may delay subsequent administration of chemotherapy for symptomatic progression in these patients [40]. Combination treatment with tamoxifen and goserelin was evaluated in two phase II, single-arm clinical trials in patients with recurrent, chemotherapy-resistant epithelial ovarian cancer. The combination of tamoxifen and goserelin was assessed by Hasan and colleagues who reported a response rate of 11.8% and stable disease for 6 months in 38.5% with a combined clinical benefit rate of 50%. The median progression-free interval was 4 months whereas the median overall survival duration was 13.6 months. Treatment-limiting toxicity was not seen in any patient in the study population [41]. In a similar trial, the same combination of tamoxifen and goserelin produced a high stable disease rate of 40%. The high stable disease rate and the minimal toxicity make the combination of hormonal treatments an attractive option for future clinical trials, including those assessing consolidation strategies [42].

There have been a small number of phase 2 trials of aromatase inhibitors in ovarian cancer [43,44]. In Smyth et al. [45] study of letrozole in unselected patients with relapsed epithelial ovarian

cancer with identification of an endocrine-sensitive subgroup with an ER histoscore of >150. That study showed statistically significant association between ER status and response to letrozole, which was not observed in the other two studies of aromatase inhibitors in this setting. This may be due to differences in technique of ER estimation, size of study, or prior exposure to hormonal agents. The preselecting of patients according to ER status results in a significant percentage of patients having benefit from anti-estrogen therapy. In single-institution, phase II study was performed in women with recurrent ER positive epithelial carcinoma of the ovary or peritoneum. All patients had measurable disease. Letrozole was administered at a dose of 2.5 mg orally once daily until disease progression or toxicity occurred. In patients with ER-positive, platinum- and taxane-resistant high-grade ovarian and primary peritoneal cancer treated with letrozole, 26% derived a clinical benefit [46].

The majority of epithelial ovarian cancer maintain expression of the androgen receptor (AR) to a higher degree than estrogen or progesterone receptors. They suggested that the AR is involved in molecular signaling in epithelial ovarian cancer. Many trials were done with compounds affecting androgen axis to assess the efficacy of androgen manipulation in epithelial ovarian cancer. Most of these trials involved patients with recurrent cancer [42]. Abiraterone, a CYP17 inhibitor, which irreversibly inhibits androgen biosynthesis, has been evaluated in a phase II study of 42 patients with recurrent epithelial ovarian cancer (CORAL study). Using a cut-off value of 10%; there were 69% of patients AR + ve. Sustained clinical response was achieved in 26% of patients. The absence of significant toxicity confirms that effective hormonal therapy using as a consolidation approach would be an attractive option [47].

Hormone therapy in granulosa cell tumor
Granulosa cell tumors (GCTs) represent 2–5% of all ovarian malignancies. Histologically classified as sex cord stromal tumors, they account for 70-85% of tumors arising from that portion of the ovary. GCTs are characterized by long natural history and their tendency to recur years after the initial diagnosis [48].

There are two distinct histological types - adult GCT (AGCT) and juvenile GCT (JGCT). AGCTs are more common and are usually seen in perimenopausal and postmenopausal women, with a peak incidence at 50-55 years. JGCTs are rare tumors, representing 5% of all GCTs and occurring in premenarchal girls [49]. IHC for inhibin appears to be the most sensitive and specific for granulosa cell tumors However, immunohistochemical positivity for inhibin is not absolutely specific for an ovarian sex cord tumor. In one report, as an example, positive IHC for inhibin was present in 94 percent of granulosa cell tumors and in 10 to 20 percent of ovarian endometrioid tumors and metastatic carcinomas to the ovary (although with significantly weaker staining intensity) [50]. About 30% of granulosa tumors ER positive and almost 100% PR positive, so hormonal agents such as progestogens or LHRH agonists have been used widely to treat these patients but they are often elderly and not suitable for aggressive chemotherapy [51,52]. Several

theories have been proposed for how hormone manipulation may inhibit tumor growth in GCTs. Possible mechanisms can be divided into three categories: (1) indirect action on tumor via suppression of gonadotropins or endogenous steroids; (2) direct effect on the tumor; and (3) a combination of the first two mechanisms [53].

A proportion of GCTs expresses receptors for follicle stimulating hormone (FSH), which has been shown to support the growth of GCTs in nude mice. Thus, hormonal therapies that can decrease gonadotropins may block the stimulatory effects on granulosa cells. GnRH agonists have previously been used in other hormonally regulated cancers, such as breast and prostate cancer [54].

To evaluate leuprolide acetate for treating refractory or persistent ovarian granulosa cell tumor (GCT), five patients who had recurrent or persistent ovarian GCT was treated with monthly intramuscular injections of a depot formulation of leuprolide acetate, 7.5 mg. Four patients had received prior cisplatin-based chemotherapy. One of these four patients also had received prior therapy with tamoxifen that had resulted in three months of stable disease. The objective response rate was 40%. Cessation of disease progression was noted in all 5 of the evaluable patients. No major side effects were noted. Leuprolide acetate thus appears to have activity in patients with refractory GCT, and it may prolong the disease progression-free interval [55].

In Kim et al. [56] case report study, a 65-yr-old multiparous woman with metastatic ovarian cancer, showed repeated recurrence and received several lines of chemotherapy and palliative RT. One month after completing radiotherapy and after three GnRH agonist injections, there are partial response was calculated as 36.5% decreased, using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, for the target lesions in the abdominal cavity, excluding the pelvic mass. With the change in the tumors, her blood estradiol level decreased. Two case series have reported durable responses to aromatase inhibitor in a total of 6 patients. All these patients had been intolerant of chemotherapy or experienced tumor progression despite receiving chemotherapy, and 2 of patients described had also previously received leuprolide. In all cases, there was evidence of complete or partial radiological response and sustained benefit on treatment for more than12 months [57]. There are number of ongoing phase II trials exploring combinations of hormonal agents with other therapeutic agents in ovarian cancer. For example, study of letrozole and everolimus, an mTOR inhibitor, in patients with platinum-resistant/refractory ovarian cancer or endometrial cancer is currently recruiting patients (NCT0218850). Also, another trial of letrozole and ribociclib (CDK4/6 inhibitor) in patients with relapsed ER-positive ovarian cancer and endometrial cancer is underway (NCT02657928) [58].

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